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RESEARCH ARTICLE

Associations between glutathione *S*-transferase π Ile^{105}Val and glyoxylate aminotransferase Pro^{11}Leu and Ile^{340}Met polymorphisms and early-onset oxaliplatin-induced neuropathy

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Key words: oxaliplatin, neurotoxicity, colorectal cancer, GSTP1 Ile^{105}Val, AGXT Pro^{11}Leu, AGXT Ile^{340}Met

Purpose: Although the risk of oxaliplatin-induced neuropathy depends on cumulative oxaliplatin dose, susceptibility to this adverse event differs greatly among patients. In this study, we investigated the associations between oxaliplatin-induced neuropathy and the following polymorphisms: glutathione *S*-transferase π (*GSTP1*) Ile^{105}Val, and glyoxylate aminotransferase (*AGXT*) Pro^{11}Leu and *AGXT* Ile^{340}Met.

Experimental Design: Eighty-two Japanese patients with histologically confirmed colorectal cancer who received at least six cycles of the modified FOLFOX6 (m-FOLFOX6) regimen were enrolled. To minimize differences in cumulative oxaliplatin dose between patients, oxaliplatin-induced neuropathy was evaluated using an oxaliplatin-specific scale during the two-week period after completion of the sixth cycle of treatment.

Results: Forty-four patients developed grade 2/3 oxaliplatin-induced neuropathy. There were more patients carrying at least one *GSTP1* ^{105}Val allele among the group with grade 2/3 neuropathy (18/44, 41%) than among the group with grade 1 neuropathy (9/38, 24%), although the difference was not statistically significant ($P = 0.098$). There were similar numbers of patients carrying at least one *AGXT* ^{105}Met allele in the grade 2/3 neuropathy (7/44, 16%) and grade 1 neuropathy groups (5/38, 13%; $P = 0.725$). The *AGXT* ^{11}Leu allele was not found in any of our patients or controls.

Conclusions: We found no significant association between oxaliplatin-induced neuropathy and the *GSTP1* Ile^{105}Val and *AGXT* Ile^{340}Met polymorphisms. Given that no *AGXT* ^{11}Leu allele was found among our study population (n = 177), evaluating this polymorphism in Japanese patients in future studies is likely to be uninformative.

Introduction

Oxaliplatin, a third-generation diaminocyclohexane platinum compound, is a key drug in the chemotherapeutic treatment of patients with advanced colorectal cancer (1-3). Oxaliplatin is widely used in palliative settings, and in recent times its efficacy in neoadjuvant and adjuvant settings has also been established, thus an increasing number of colorectal cancer patients are receiving this drug (4, 5). Oxaliplatin often causes neuropathy, which limits the ongoing use of this drug in spite of its wide range of efficacy. The risk of developing oxaliplatin-induced neuropathy depends on cumulative oxaliplatin dose (2, 6, 7). However, susceptibility to oxaliplatin-induced neuropathy differs greatly among patients. Some patients suffer from persistent neuropathy for more than 2 years after withdrawal of oxaliplatin, whereas others can tolerate a cumulative oxaliplatin dose of more than 800 mg/m^2 without experiencing neuropathy (6-9). Since there is currently no effective treatment for oxaliplatin-induced neuropathy, risk assessments for this adverse event using a pharmacogenetic approach are clinically valuable.

To date, several genes have been identified as being of interest in the context of the efficacy and toxicity of oxaliplatin. Glutathione *S*-transferase π (*GSTP1*) is a xenobiotic-metabolizing enzyme involved in the detoxification of a variety of chemotherapeutic drugs, including platinum derivatives (10). Rs1695, a

non-synonymous single nucleotide polymorphism (SNP) of *GSTP1*, converts Ile to Val at codon 105 and reportedly alters the enzymatic activity of the molecule (10-13). Given that altered *GSTP1* enzyme activity is likely to affect the detoxification of platinum drugs, the association between the *GSTP1* Ile^{105}Val polymorphism and clinical response to platinum-based chemotherapy has been examined (14-28). However, few of these studies were designed to evaluate oxaliplatin-induced neuropathy as a primary endpoint. In one such study, that by Lecomte et al., it was found that grade 3 neuropathy was significantly more frequent among patients harboring the homozygous *GSTP1* ^{105}Ile allele than among patients with other genotypes. These authors hypothesized that the GSTP1 ^{105}Ile protein weakens the cell's defenses against oxaliplatin neurotoxicity via inhibition of c-Jun NH_2-terminal kinase activity (17). The results of several other studies support this hypothesis (25, 27), whereas other groups have reported no significant association between this genotype and oxaliplatin neurotoxicity (24, 26) or have obtained contradictory results (21, 28). Other experimental findings that indirectly challenge the view of Lecomte et al. are that the GSTP1 ^{105}Val protein is a less potent detoxifier of carcinogens than the GSTP 1 ^{105}Ile protein (13) and that patients with the Val/Val genotype have been found to receive significant survival benefit from oxaliplatin (14). Thus, the role of the *GSTP1* Ile^{105}Val polymorphism in predicting oxaliplatin-induced

neuropathy is still controversial.

Oxaliplatin affects neural voltage-gated sodium channels indirectly via one of its metabolites, oxalate (29, 30). Based on the fact that glyoxylate aminotransferase (AGXT) is involved in the oxalate metabolic pathway (31), Gamelin et al. hypothesized that alterations in *AGXT* genotype and therefore enzyme activity due to *AGXT* genotype could theoretically affect the likelihood of oxaliplatin-induced neuropathy. In fact, they found that the *AGXT* Pro^{11}Leu and Ile^{340}Met minor polymorphisms are significantly associated with a higher risk of oxaliplatin-induced neuropathy (24).

However, all the above-mentioned studies were carried out using Caucasian patient populations, and to date there have been no such studies performed for Asian patients. There exist considerable interethnic differences in genotype frequency, which can greatly affect the results of pharmacogenetic analyses. For example, the *UGT1A1*28* marker is known to vary markedly between ethnic groups (32-34).

In the present study, we investigated the association between the *GSTP1* Ile^{105}Val, *AGXT* Pro^{11}Leu and *AGXT* Ile^{340}Met polymorphisms and the development of oxaliplatin-induced neuropathy in Japanese colorectal cancer patients. To minimize differences in cumulative oxaliplatin dose, we studied oxaliplatin-induced neuropathy that developed in the 2 weeks after completion of the sixth cycle of m-FOLFOX6.

Patients and Methods

Patients

Between October 2005 and December 2008, a total of 174 patients with histologically confirmed colorectal cancer received at least six cycles of the m-FOLFOX6 regimen at two medical centers. Eighty-two patients (the patients' characteristics are summarized in Table 1) were enrolled in this cohort study. The remaining patients were excluded because they died (n = 60), were referred to another hospital (n = 10), or were lost to follow-up (n = 22) before we could obtain informed consent or a blood sample. The local ethics committees of both centers approved the study protocol. All patients enrolled in this study provided written informed consent. Patient registration and data management were conducted at a data center at Kyoto University Hospital (Translational Research Center). Forty-eight of the 82 patients were chemo-naïve and the others had previously undergone at least one chemotherapy regimen other than oxaliplatin-based chemotherapy before m-FOLFOX6 (see Table 1 for details). None of the patients had a history of diabetic neuropathy, but two patients had a history of spondylosis. The m-FOLFOX6 regimen consists of 85 mg/m^2 oxaliplatin plus a 400 mg/m^2 bolus of 5-fluorouracil and 200 mg/m^2 L-leucovorin on day 1, and thereafter a 46-h infusion of 2400 mg/m^2 5-fluorouracil every 2 weeks (35). The dose and schedule for m-FOLFOX6 were

adjusted at the discretion of individual physicians according to baseline bone marrow function or the occurrence of adverse events during the previous cycle. Bevacizumab was concomitantly administered to two patients. Blood tests and physical examinations, including evaluation of oxaliplatin-induced neuropathy, were performed before each cycle. Instances of oxaliplatin-induced neuropathy that occurred during the two weeks after completion of the sixth cycle of m-FOLFOX6 were graded using an oxaliplatin-specific scale (grade 1: paresthesia, dysesthesia of short duration; grade 2: paresthesia, dysesthesia persisting between cycles; grade 3: paresthesia, dysesthesia causing functional impairment) (6, 36). In this study, we classified patients without paresthesia or dysesthesia into the grade 1 group.

DNA extraction and genotyping

Genomic DNA was extracted from whole blood using the phenol-chloroform extraction method and stored at 4°C until use. The *GSTP1* Ile^{105}Val, *AGXT* Pro^{11}Leu and *AGXT* Ile^{340}Met genotypes were determined by using a fluorescence quenching probe (QProbe, Bex Co., Ltd., Tokyo, Japan) (37, 38). Briefly, a QProbe contains cytosine at its 5' or 3' end, which is labeled with a fluorophore that is quenched by guanine. When a QProbe hybridizes with the target DNA, its fluorescence is quenched by the guanine in the target that is complementary to the modified cytosine. By monitoring fluorescence intensity,

each genotype can be determined. The frequencies of the three SNPs in the general Japanese population were also examined using DNA samples from healthy Japanese volunteers in Pharma SNP Consortium (Tokyo, Japan) (39). This population is referred to hereafter as the control Japanese population. The investigators performing the genetic analysis were blinded to the patients' characteristics and clinical condition. The characteristics and frequencies of the studied polymorphisms are shown in Table 2.

Statistical analysis

The primary endpoint of the study was the association between genotype distribution and the occurrence of grade 2/3 oxaliplatin-induced neuropathy during the 2 weeks after completion of the sixth cycle of m-FOLFOX6 treatment. The planned sample size (n=82) was specified in the protocol to provide 80% power to detect an odds ratio (OR) of 5.4. The calculations were based on a previous finding that the OR of developing grade 3 oxaliplatin-induced neuropathy in a patient without the *GSTP1* ^{105}Val allele was 5.54 (17). We estimated that the frequency of patients in our Japanese population with at least one *GSTP1* ^{105}Val allele was 21% and used estimated incidences of grade 2/3 oxaliplatin-induced neuropathy after the first six cycles of mFOLFOX6 for patients with and without a *GSTP1* ^{105}Val allele of 30% and 70%, respectively. Statistical analysis was performed using a two-sided χ^2/Fisher's exact test with a significance level of 5%, and

quantified by calculating ORs with 95% confidence intervals (95% CI). All statistical analysis was conducted using SAS (version 9.13, SAS Institute Inc., Cary, NC)

Results

Patient characteristics are summarized in Table 1. The median cumulative dose of oxaliplatin was 510 mg/m^2 (range, 336-510 mg/m^2). Although some patients received a lower cumulative dose than expected, the most common cause of dose adjustment was neutropenia and none of our patients underwent a dose reduction because of neurotoxicity. Forty-four patients (54%) developed grade 2/3 oxaliplatin-induced neuropathy (as scored using the oxaliplatin-specific scale) during the 2 weeks after completion of the sixth cycle of m-FOLFOX6. No significant differences in age, gender or cumulative oxaliplatin dose were observed between the group of patients with grade 2/3 neuropathy and those with grade 1 neuropathy (Table 3).

We performed genotyping analysis for the rs1695, rs34116584 and rs4426527 SNPs, which correspond, respectively, to the *GSTP1* Ile^{105}Val, *AGXT* Pro^{11}Leu and *AGXT* Ile^{340}Met polymorphisms. We performed this analysis for 44 patients with grade 2/3 neuropathy (group A) and 38 patients with grade 1 neuropathy (group B). The frequencies of the variant allele in rs1695 (G), corresponding to *GSTP1*^{105}Val, were 0.216 for group A and 0.132 for group B. Although the frequency was higher in group A, the difference was not statistically significant (P = 0.158) (Table 2). The frequency of allele G in the control Japanese population was 0.147, which is similar to that of group B.

When a dominant model for the variant allele (G) was applied for comparison, the number of patients carrying at least one variant allele was higher in group A (18/44, 41%) than in group B (9/38, 24%) although the difference was not statistically significant (P = 0.098) (Table 2). A similar trend was observed when the same comparison between group A and the control Japanese population was performed (P = 0.080) (Table 2).

The G allele of SNP rs4426527, corresponding to *AGXT* Ile^{340}Met, was present at frequencies that were not significantly different in group A and group B (P = 0.553) (Table 2). The T allele of SNP rs34116584, corresponding to *AGXT* ^{11}Leu, was absent in group A, group B and the control Japanese population (n = 177, data not shown). The frequencies of *GSTP1* Ile^{105}Val and *AGXT* Ile^{340}Met were in Hardy-Weinberg equilibrium.

Discussion

In this study, to minimize differences in cumulative oxaliplatin dose among patients, we attempted to evaluate oxaliplatin-induced neuropathy during the two weeks after completion of the sixth cycle of m-FOLFOX6. As a result, we evaluated early-onset neuropathy rather than the most severe grade of neuropathy that is associated with oxaliplatin.

Lecomte et al. reported that grade 3 oxaliplatin-induced neuropathy, as scored using the oxaliplatin-specific scale, was significantly more frequent among patients harboring the homozygous *GSTP1* ^{105}Ile allele (17). Our planned sample size of 82 was based on these findings. In contrast to the findings of Lecomte et al., we found that grade 2/3 neuropathy was more common among patients harboring at least one *GSTP1*^{105}Val allele, although the difference was not statistically significant (OR, 2.23; 95% CI, 0.86-5.82; P = 0.098; Table 2). There are several possible reasons for this discrepancy between the outcomes of two studies. As mentioned above, our findings reflect our focus on early-onset neuropathy, while Lecomte et al. studied the most severe grade of neuropathy experienced during oxaliplatin treatment. Our findings are in line with those of Grothey et al., who determined that patients harboring at least one *GSTP1*^{105}Val allele were more likely to experience early-onset oxaliplatin-induced grade 2/3 neuropathy (28). Because

Grothey et al. studied neuropathy that developed before the cumulative oxaliplatin dose reached 600 mg/m^2, their approach is more similar to ours than that of Lecomte et al. Since functional impairment due to oxaliplatin neuropathy does not necessarily develop in a progressive manner but develops suddenly in some patients (40), it is possible that those who are prone to developing early-onset neuropathy have different genotypes from those who suffer from functional impairment due to oxaliplatin neuropathy.

Genetic differences related to ethnic background may also be a reason for the differences between the present results for Japanese patients and the previous results for Caucasian patients. In particular, because of the very low frequency of the *GSTP1* 105 Val/Val genotype among our patients as well as the control Japanese population, we cannot accurately assess the role of this genotype in predicting the likelihood of oxaliplatin-induced neuropathy. Previously published data on the *GSTP1* Ile^{105}Val polymorphism and oxaliplatin neurotoxicity are summarized in Table 4.

There has been only one prior study in which the associations between *AGXT* genotypes and oxaliplatin-induced neuropathy have been investigated (24). In contrast to the findings of Gamelin et al., we did not see any significant association between oxaliplatin-induced neuropathy and the *AGXT* Ile^{340}Met polymorphism. This might also be explained by differences in genetic background. In particular, no patients harbored the

AGXT ^{11}Leu allele in our study, whereas 30% of patients were found to harbor at least one *AGXT* ^{11}Leu allele in a Caucasian patient population (24). In contrast to other clinical responses, such as tumor shrinkage or neutropenia, oxaliplatin-induced neuropathy is minimally affected by concomitantly administered drugs or genetic changes in the tumor cell, so genetic polymorphisms are particularly relevant in the context of susceptibility to oxaliplatin-induced neuropathy. In future pharmacogenetic studies, in order to obtain the most consistent results, we recommend that early-onset neuropathy be evaluated separately from the most severe neuropathy and inter-patient differences in cumulative oxaliplatin dose be minimized.

In summary, we found no significant associations between oxaliplatin-induced neuropathy during the 2-week period after the completion of six cycles of m-FOLFOX6 and the *GSTP1* Ile^{105}Val and *AGXT* Ile^{340}Met polymorphisms in Japanese colorectal cancer patients. Since no patients harbored the *AGXT* ^{11}Leu allele in the present study, it seems likely that evaluating this polymorphism in Japanese patients in future studies will not be informative.

Conflict of interest statement

None declared

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Table 1. Patient characteristics (n = 82)

Variable	n (%)
Gender	
Male	51 (62)
Female	31 (38)
Age (years)	
Median	64
Range	41-80
Location of primary lesion	
Colon	47 (57)
Rectum	35 (43)
Histology	
Well-differentiated	11 (13)
Moderately differentiated	58 (71)
Poorly differentiated	1 (1)
Other	12 (15)
History of prior chemotherapy	
None	48 (59)
Yes	34 (41)
Previous chemotherapy regimen*	
UFT/Uzel	17
5-FU/leucovorin	9
TS-1	7
FOLFIRI	5
UFT	5
Other	3
Cumulative oxaliplatin dose (mg/m^2)	
Median	510
Range	336-510

* Several patients received more than one regimen

Table 2. Genotype and allele frequencies for the investigated polymorphisms

Polymorphism		rs ID	Nucleotide		Amino acid		Sample set	Genotype distributions (%)			Freq. A2	*P*-value[a]
			ref. (A1)	var. (A2)	ref.	var.		A1/A1	A1/A2	A2/A2		
GSTP1	Ile[105]Val	rs 1695	A	G	Ile	Val	Grade 2/3	26 (59.1)	17 (38.6)	1 (2.3)	0.216	
							Grade 1	29 (76.3)	8 (21.0)	1 (2.6)	0.132	0.158
							Control[b]	68 (73.9)	21 (22.8)	3 (3.2)	0.147	0.155
AGXT	Ile[340]Met	rs 4426527	A	G	Ile	Met	Grade 2/3	37 (84.1)	6 (13.7)	1 (2.3)	0.091	
							Grade 1	33 (86.8)	5 (13.2)	0	0.066	0.553
							Control[b]	82 (91.1)	8 (8.9)	0	0.044	0.132

[a]*P*-values are calculated for grade 2/3 vs. grade 1 or grade 2/3 vs. control.
[b]a sample set representing a control population of healthy Japanese subjects was used.

[c]Odds ratios are calculated for grade 2/3 vs. grade 1 or grade 2/3 vs. control.

Table 2 continued

Polymorphism		Genotype distribution		*P*-value[a]	Odds ratio[c] (95% CI)	References
		A1/A1	A1/A2+A2/A2			
GSTP1 Ile[105]Val	Grade 2/3	26	18			
	Grade 1	29	9	0.098	2.23 (0.86 – 5.82)	14, 16
	Control[b]	68	24	0.080	1.96 (0.92 – 4.20)	
AGXT Ile[340]Met	Grade 2/3	37	7			
	Grade 1	33	5	0.725	1.25 (0.36 – 4.31)	23
	Control[b]	82	8	0.226	1.94 (0.66 – 5.74)	

Table 3. Association between clinical variables and genotypes and oxaliplatin-induced neuropathy

	n (%)			
	Grade 1	Grade 2	Grade 3	*P**
Age (years)				
<60	15 (62)	9 (38)	0 (0)	0.13
≥60	23 (40)	34 (59)	1 (2)	
Gender				
Male	27 (53)	24 (47)	0 (0)	0.11
Female	11 (36)	19 (61)	1 (3)	
Cummulative oxaliplain dose (mg/m^2)				
<510	18 (49)	18 (49)	1 (3)	0.50
510	20 (44)	25 (56)	0 (0)	
GSTP1 Ile^{105}Val				
Ile/Ile	29 (52)	26 (47)	0 (0)	0.16
Ile/Val	8 (32)	16 (64)	1 (4)	
Val/Val	1 (50)	1 (50)	0 (0)	
AGXT Ile^{340}Met				
Ile/Ile	33 (48)	36 (51)	1 (1)	1.00
Ile/Met	5 (45)	6 (55)	0 (0)	
Met/Met	0 (0)	1 (100)	0 (0)	

*Fisher's exact test

Table 4. Findings from published studies on *GSTP1* Ile^{105}Val and oxaliplatin-induced neuropathy among patients with colorectal cancer

Study	Year	Sample size	Ethnicity	Regimen	Cumulative oxaliplatin dose (mg/m^2)	Genotype distributions (%)			Genotype associated with frequent neuropathy	*p*-value
						A1/A1	A1/A2	A2/A2		
Lecomete et al.[17]	2005	64	Caucasian*	Mainly FOLFOX4 (72%)	≥500	39 (61)	20 (31)	5 (8)	A1/A1	0.02
Grothey et al.[28]	2005	288	Caucasian	FOLFOX4	≤600	120 (42)	130 (45)	38 (13)	A1/A2 + A2/A2	0.03
Ruzzo et al.[21]	2007	166	Caucasian	FOLFOX4	N/A	92 (55)	62 (37)	12 (8)	A2/A2	< 0.001
Gamelin et al.[24]	2007	122	Caucasian	FOLFOX4	255–2125	54 (44)	56 (46)	12 (10)	ns	ns
Pare et al.[25]	2008	126	Caucasian	FOLFOX4	≥510	44 (35)	49 (49)	20 (16)	A1/A1	0.08
Kweekel et al.[26]	2009	56	Caucasian	XELOX	≥500	25 (45)	25 (45)	6 (11)	ns	ns
Current study	2009	82	Japanese	m-FOLFOX6	≤510	55 (67)	25 (30)	2 (2)	A1/A2 + A2/A2	0.1

*Except four African patients and one Asian patient; N/A, not applicable; ns, not significant; XELOX regimen consists of 130 mg/m^2 oxaliplatin plus 1000 mg/m^2 capecitabine b.i.d every 3 weeks.